John von Neumann Institute for Computing

Improved Hydrogen Bond Potentials to Assess *in Silico* Protein Folding

M. G. Wolf, J. Vreede, P. G. Bolhuis, S. W. de Leeuw

published in

From Computational Biophysics to Systems Biology (CBSB08),
Proceedings of the NIC Workshop 2008,
Ulrich H. E. Hansmann, Jan H. Meinke, Sandipan Mohanty,
Walter Nadler, Olav Zimmermann (Editors),
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. **40**, ISBN 978-3-9810843-6-8, pp. 413-416, 2008.

http://www.fz-juelich.de/nic-series/volume40

Improved Hydrogen Bond Potentials to Assess *in Silico* Protein Folding

Maarten G. Wolf[1], **Jocelyne Vreede**[2], **Peter G. Bolhuis**[2], **and Simon W. de Leeuw**[1]

[1] Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands
E-mail: m.g.wolf@tudelft.nl

[2] University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands

Introducing backbone hydrogen bond potentials that alternate between attraction and repulsion, forcing a fast reordering, leads to fast *in silico* folding of small proteins. However thermodynamic properties cannot be extracted from these simulations and they are not suitable for use in generalized ensemble methods. In this paper we address the development of a hydrogen bond potential that is energy conserving and time-reversible, without loss of efficiency.

1 Introduction

Computational modeling at atomic resolution has the potential to reveal properties that are inaccessible to experiments, but its application is amongst others limited by a sampling problem. This is a consequence of the rugged free-energy landscape observed in detailed protein models.

Hydrogen bonds make an important contribution to the free-energy landscape of a protein and are required to compensate the free-energy cost of burying (partially) charged groups.[1] Although there is no net free energy gain upon hydrogen bond reordering, the associated barrier of 2-3 kT[2] contributes strongly to the ruggedness of the free-energy landscape.

In a previous study we showed that the sampling problem can be reduced by facilitating barrier crossings, in particular those associated with hydrogen bond formation/breaking. We introduced hydrogen bond potentials that alternate between attraction and repulsion (AHBP) forcing a fast reordering of the backbone hydrogen bonds which leads to fast in silico folding of small proteins.[3]

However simulations with these alternating hydrogen bond potentials are not time-reversible and they do not conserve energy. Hence thermodynamic properties cannot be extracted from these simulations and they are not suitable for use in generalized ensemble methods. In this paper we address the development of a continuous hydrogen bond potential that is energy conserving and time-reversible, without loss of efficiency.

2 Continuous Hydrogen Bond Potential

There are a number of requirements that must be satisfied in the new hydrogen bond potential. Firstly, in an md simulation the energy needs to be conserved in order to acquire a proper sampling of the free-energy landscape. For the individual hydrogen bond potentials this can easily be satisfied by expressing the distance interaction function I_d and the angle interaction function I_θ as a cubic spline.

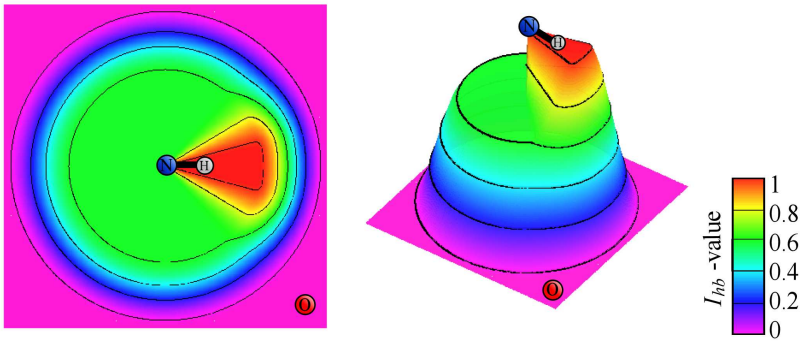

Figure 1. **The interaction function I_{hb} (eq 2) shown for the oxygen position in a plane around the N-H atoms displayed in topview (left) and sideview (right).**

Secondly, the energy and the derived forces of the hydrogen bond potential must result in efficient hydrogen bond reordering. Because reordering mainly requires a change in distance a larger weight for the distance relative to the angle interaction is desired. Within the observation that the angle potential only has meaning at short separation of donor and acceptor the range of the distance and angle function is set to $1.0 - 0.0$ and $1.0 - 0.6$, respectively.

Finally, a hydrogen bond is very selective, usually having only one partner (with occasionally a second), restricting the number of potentials per donor (acceptor) to one. To avoid the need for native state input the partner must be selected based on the conformation in the simulation. Therefore we choose for every donor (acceptor) the partner with the highest value of the hydrogen bond interaction function I_{hb} every time step. In this way the energy is conserved because a switch of partners takes place when the energies are equal. Since the hydrogen bond potential is an interaction function also linear momentum is conserved and only angular momentum is not conserved.

The following continuous hydrogen bond potential V_{hb} (CHBP) is consistent with these requirements.

$$V_{hb}(r) = fc \cdot \sum_{k}^{A,D} \max\{I_{hb}(r_k, r_l)\}_{l \in A,D} \tag{1}$$

$$I_{hb}(r_k, r_l) = I_d(r_k, r_l) \cdot I_\theta(r_k, r_l) \tag{2}$$

$$I_d(r_k, r_l) = \begin{cases} 1 & r_{kl} < r_{min} \\ \frac{2(r_{kl}-r_{min})^3}{(r_{max}-r_{min})^3} + \frac{3(r_{kl}-r_{min})^2}{(r_{max}-r_{min})^2} + 1 & r_{min} \le r_{kl} < r_{max} \\ 0 & r_{max} \le r_{kl} \end{cases} \tag{3}$$

$$I_\theta(\theta_k, \theta_l) = \begin{cases} 1 & \theta_{kl} < \theta_{min} \\ 0.4 \cdot [\frac{2(\theta_{kl}-\theta_{min})^3}{(\theta_{max}-\theta_{min})^3} + \frac{3(\theta_{kl}-\theta_{min})^2}{(\theta_{max}-\theta_{min})^2}] + 1 & \theta_{min} \le \theta_{kl} < \theta_{max} \\ 0.6 & \theta_{max} \le \theta_{kl} \end{cases} \tag{4}$$

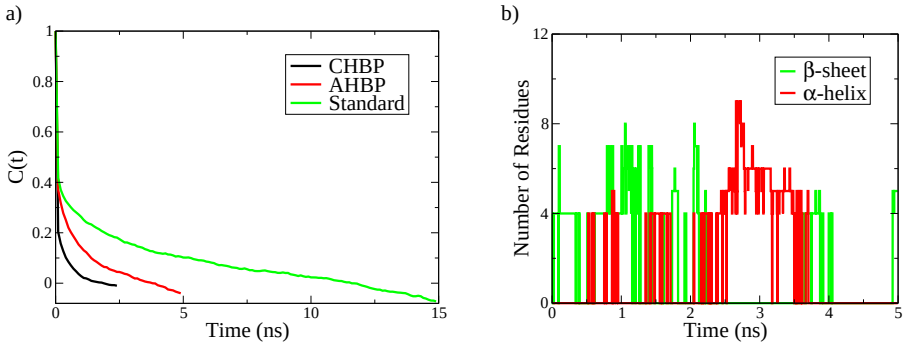

Figure 2. **Effectiveness of the hydrogen bond potentials.** a) The auto correlation function shows the hydrogen bond lifetime for the different simulations. b) The secondary structure formed in a small simulation with the new continuous hydrogen bonds potentials.

with V_{hb} the total potential energy of the hydrogen bond potentials, fc the force constant, r the distance between the donor and acceptor , θ the N-H-O angle and k and l indices of the backbone donor (D) and acceptor (A) atoms.

The parameters for the hydrogen bond potentials were chosen to affect hydrogen bonds that are (very) weak for minimum interference to the system and to leave potentially native hydrogen bonds undisturbed. The minimum and maximum cutoff distances were 0.35 nm and 0.40 nm between the donor and acceptor with a force constant of 50 for the repulsive stage and 0.23 and 0.40 nm between the hydrogen and acceptor with a force constant of -50 for the attractive stage. In both stages the mimimum and maximum N-H-O angle cutoff were 100 and 150.

3 Validation

To validate the new hydrogen bond potential we will show that the requirements 1) energy conservation, 2) selective and 3) effective are satisfied. Therefore we performed NVE simulations with an attractive, with a repulsive and without the hydrogen bond potentials. For these simulations we found a fluctuation of $3.1,\ 4.2$ and $1.8\ kJ\,mol^{-1}$, respectively, around the average total energy $101 \cdot 10^3\ kJ\,mol^{-1}$. This is $\pm 2\%$ of the kinetic and potential energy fluctuation. For all simulations the drift was $-5.7\,kJ\,mol^{-1}\,ps^{-1}$. Within the accuracy of the md algorithm the potentials are thus energy conserving. The energy conservation also shows that a switch of hydrogen bond partners, introducing selectivity, is allowed.

To test the effectiveness of the new hydrogen bond potential we performed NVT simulations where the hydrogen bond potentials are changed every ps in the order attractive-nopotential-repulsive-nopotential-attractive-etc. The effectiveness of these potentials can be expressed as the speed of hydrogen bond reordering, which depends on the hydrogen bond lifetime and the average number of hydrogen bonds. The hydrogen bond lifetime is related to the intramolecular hydrogen bond autocorrelation function, where a faster decrease in the autocorrelation functions indicates a shorter lifetime. From fig. 2a this leads to the following relation between the hydrogen bond lifetime τ_{hb} of the different simulations: $\tau_{hb,CHBP} < \tau_{hb,AHBP} < \tau_{hb,standard}$. The average number of intramolecular

hydrogen bonds is 4.1, 4.7 and 3.9 for the CHBP, AHBP and standard simulation, respectively. These results indicate an even faster hydrogen bond reordering with the new hydrogen bond potentials.

The effectiveness can also be expressed as the speed of forming different secondary structure elements. In fig. 2b the occurrence of α-helix and β-sheet during a simulation with CHBP changing between attrative and repulsive is shown. Clearly both secondary structure elements are easily formed with this potential.

4 Outlook

In this paper we have shown that an energy conserving hydrogen bond potential can result in quick sampling of the conformational space of a polyalanine when the CHBP is changed between attractive and repulsive. However thermodynamic properties can only be extracted from these simulations if this change is Boltzmann weighted. Consequently a method that changes the potentials while maintaining detailed balance, like for example replica exchange, can reveal thermodynamic properties (J. Vreede and M. Wolf, in preparation).

5 Simulation Details

All simulations were performed using the GROMACS[4] software package version 3.3.1 extended with the hydrogen bond potentials using the GROMOS96 43a1 forcefield.[5] A timestep of 2 fs for NVT and 0.1 fs for NVE was used, with all bonds constrained using the LINCS algorithm. Van der Waals interactions were ignored outside a cut-off of 1.2 nm. Electrostatic interactions were treated with the PME method applying a real-space cutoff of 0.9 nm. In the NVT simulation the system temperature was coupled to a Berendsen thermostat.

The starting structure of the simulations is a random collapsed coil poly alanine of 16 residues, dissolved in a box of approximately 2000 SPC water to obtain a density of 0.97 kg/l. Initial velocities were generated randomly to get a system at 300 K, which was simulated under NVT conditions for 1 ns to equilibrate before production runs were performed.

Acknowledgments

This work was funded by the Netherlands Organization for Scientific Research NWO (grant number 635.100.012, program for computational life sciences).

References

1. A. Fernandez, et.al. FEBS Letters **536**, 187-192, 2003.
2. D. van der Spoel, et.al. J. Phys. Chem. B **110**, 4393–4398, 2006.
3. M. G. Wolf and S. W. de Leeuw, Biophys. J. **94**, 3742-3747, 2008.
4. D. van der Spoel, et.al. J. Comp. Chem. **26**, 1701-1718, 2005.
5. W.F. van Gunsteren, et.al. *Biomolecular simulation: the GROMOS96 manual and user guide.* (Hochschulverlag AG an der ETH Zürich, Zürich, Switzerland (1996)).